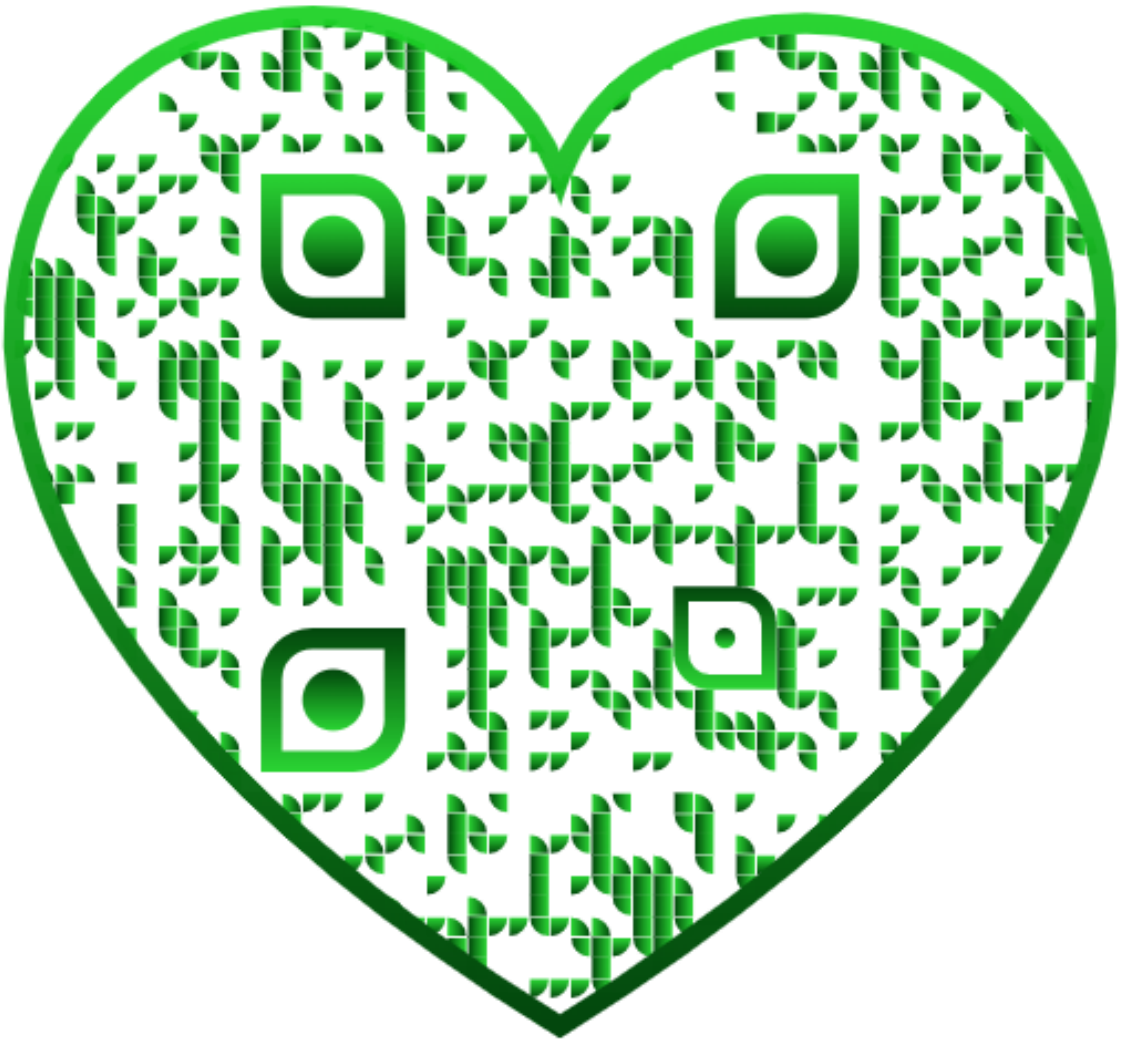
1. Semi-Solid Dosage Forms

- **Ointment**
- **Pastes**
- **Jellies and gels**
- **Creams**



- Semisolid dosage forms are dermatological products of semisolid **consistency** and applied to skin for:
  - Therapeutic
  - Protective action
  - Cosmetic function (Emolliency or Lubrication)
- Semisolid dosage forms are traditionally used for treating topical ailments.
- The vast majority of them are meant for **skin applications**. They are also used for treating ophthalmic, nasal, buccal, rectal, and vaginal ailments.

- Various categories of drugs can be incorporated into these products
  - Antibacterials, antifungals, antivirals, antipruritics, local anesthetics, anti-inflammatories, analgesics, keratolytics, astringents, and mydriatic agents
- Drugs incorporated into semisolids either show their activity on the surface layers of tissues or penetrate into internal layers to reach the site of action.
  - For example, an antiseptic ointment should be able to penetrate the skin layers and reach the deep - seated infections in order to prevent the growth of microbes and heal the wound

- Ideal properties of semisolid/dermatological preparations include:
  - Smooth texture
  - Elegant in appearance
  - Non dehydrating
  - Non gritty
  - Non greasy and Non staining
  - Non hygroscopic
  - Non irritating
  - Do not interfere with skin functioning
  - Miscible with skin secretion
  - Have low sensitization index
  - Easily applicable, & easily washability
  - Stable under various conditions

The Human Skin

- The skin provides protection and receives sensory stimuli from the environment
- The skin is the most extensive and readily accessible organ of the body
- In an average adult, it covers a surface area of over 2 m^2 and receives about 1/3 of the blood circulation
- The skin is elastic and quite rugged despite the fact that it is only approximately 3 mm thick
- It consists of three anatomical layers, the epidermis, the dermis and a subcutaneous fat layer

Epidermis

- The epidermis is a thin, dry and tough outer protective outer layer
- It forms a barrier to water, electrolyte and nutrient loss from the body,
  - It is also responsible for limiting the penetration of water and foreign substances from the environment into the body.
- Damage or removal of the epidermis allows diffusion of small water-soluble nonelectrolytes to occur approximately 1000 times faster than in the intact skin
- The epidermis is made up of two layers; Stratum germinativum, which is living, and an outer dead layer called the Stratum corneum

- The primary cell type in the stratum germinativum is the corneocyte or keratinocyte, which grows from the basal layer outwards to the skin surface.
  - The journey to the surface takes between 12 to 14 days
  - During this time the cells synthesize the various proteinaceous materials called keratin,
  - And they become thin, hard and dehydrated and begin to die
- These cells, together with intercellular lipids synthesized by the keratinocyte, form the outer stratum corneum (SC) or horny layer

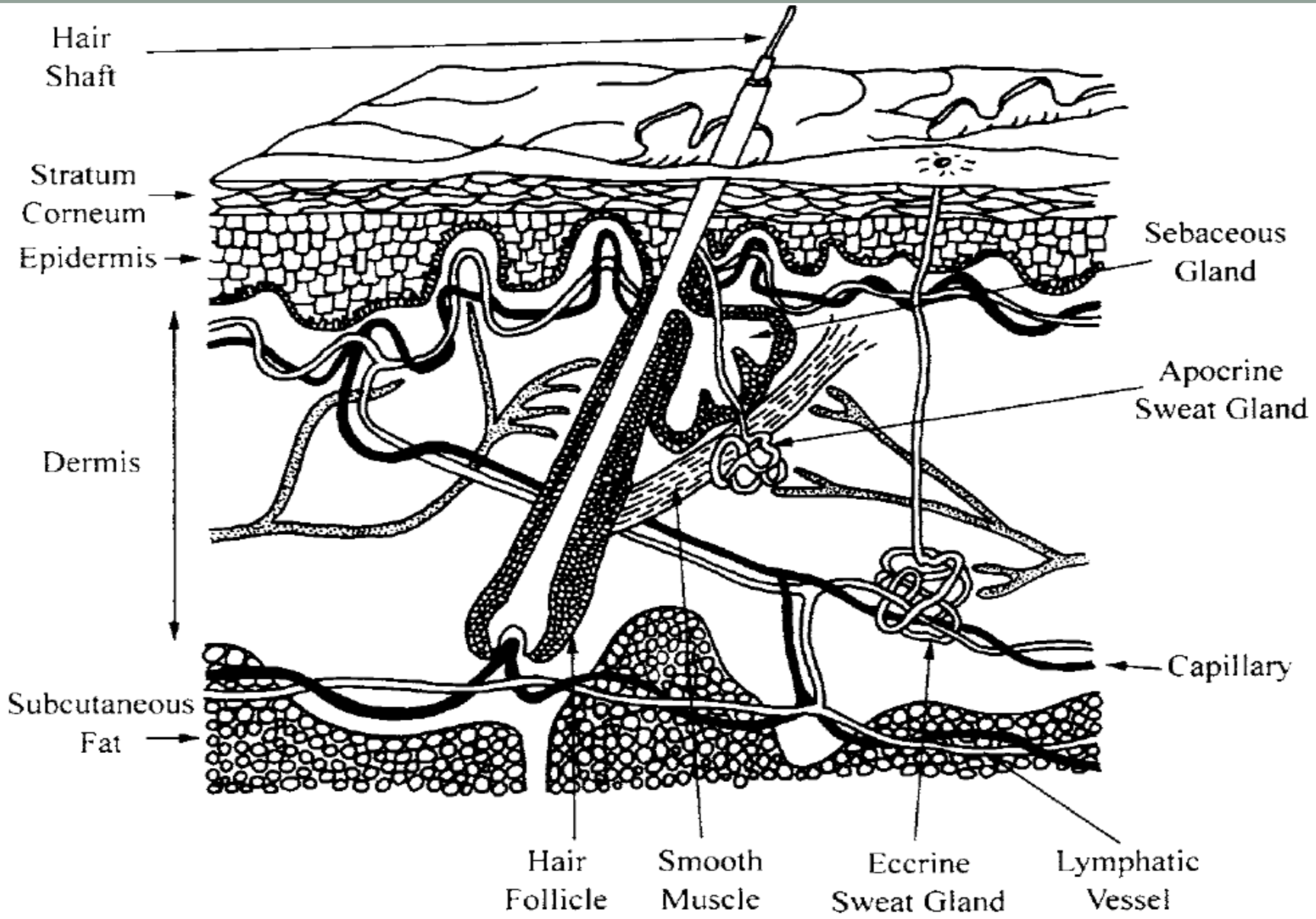


Fig. Schematic representation of the human skin

- The SC is the primary protective layer and consists of eight to sixteen layers of flattened, stratified and fully keratinised dead cells
- The water content of the normal SC is 15 to 20% of its dry weight, but when it becomes hydrated it can contain up to 75% water.
- Because the SC is the main barrier to drug absorption and its structure has been closely studied.
  - The most widely used description of the SC is the '**bricks and mortar**' model.
  - There is no direct hydrophilic path since the lipid (mortar) effectively 'insulates' the keratinocytes (bricks) from each other.

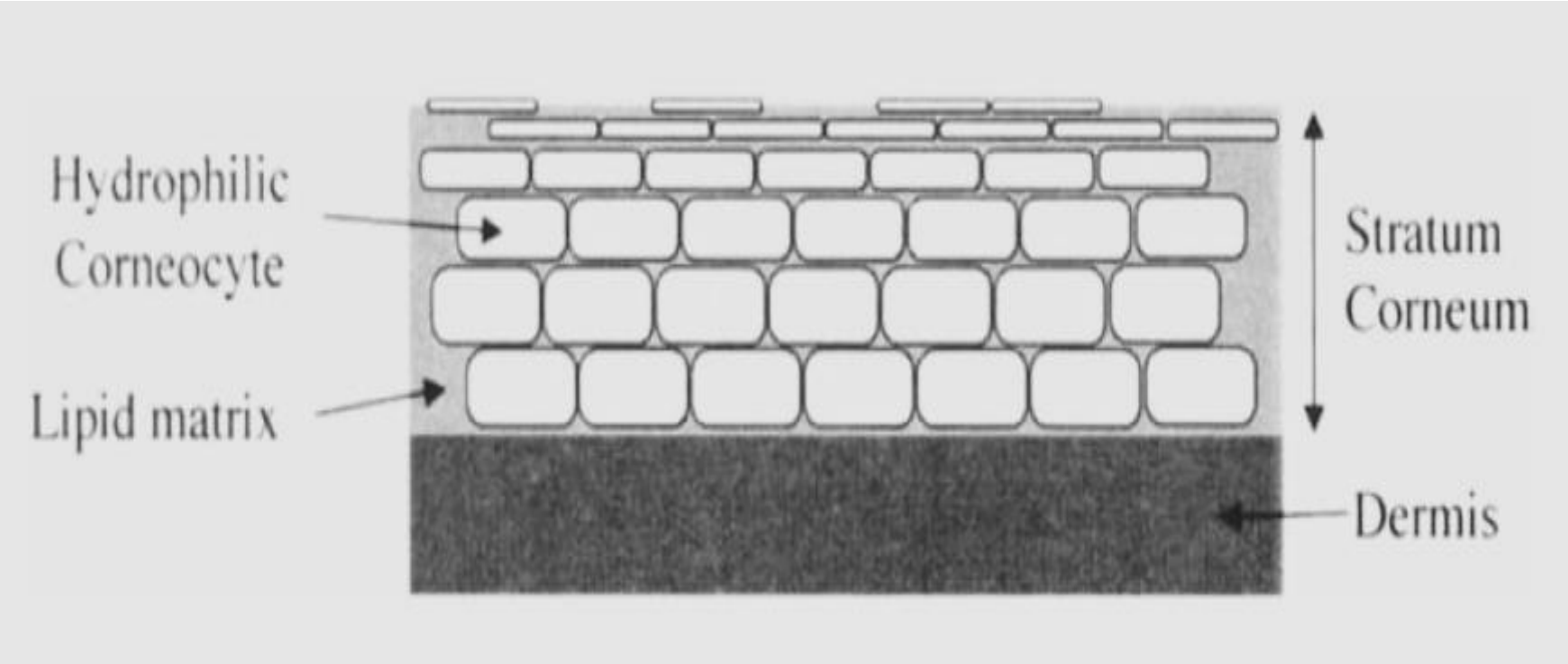


Fig. 'Bricks and mortar' model of the SC

Dermis

- The dermis is a fibrous layer which supports and strengthens the epidermis.
- It ranges from 2–3 mm thick and in man constitutes between 15% to 20% of the total body weight.
- The dermis consists of a matrix of loose connective tissue composed of fibrous protein collagen, embedded in an amorphous ground substance (water, ions, and complex carbohydrates).
- The dermis contains blood vessels, nerves, hair follicles, sebum and sweat glands.

- Three different types of cells are scattered throughout the dermis.
  i. Fibrocytes which synthesize collagen, elastin, and ground substance,
  ii. Histiocyte which are a type of macrophage, and
  iii. Mastocytes, or mast cells which are located near blood vessels; they release histamine in response to irritation, fever, oedema, and pain

Subcutaneous fat layer

- The subcutaneous fat layer (**hypodermis**) acts both as an insulator, a shock absorber, reserve depot of calories and supplier of nutrients to the other two layers.
- It is composed of loose, fibrous connective tissue which contains fat and elastic fibers.
- It is generally considered that the drug has entered the systemic circulation if it reaches this layer;
  - However, the fat deposits may serve as a deep compartment for the drug and this can delay entry into the blood.

Hair

- The hair shaft consists of differentiated horny cells and it is the only part which breaks the surface of the skin.
- Hair follicles have a diameter of approximately 70 μm and occur at fixed intervals, and hence their separation increases during growth.
- The density of hair varies over the body surface and it is normally absent from certain areas such as the lips and palms.
- The extent of hair growth plays an important role in fastening a transdermal delivery system to the skin.

Sebaceous glands

- Sebaceous glands vary in size from between 200 to 2000 μm in diameter and are found in the upper third of the hair follicle.
- Sebaceous glands secrete sebum into the hair follicle, which eventually ends up on the surface of the skin.
- Sebum consists, on average, of 58% triglycerides, 26% waxy esters, 12% squalene, 3% cholesteryl esters and 1% cholesterol.
- The lipids maintain a pH of about 5 on the skin surface, and can cause problems for the adhesives in transdermal delivery systems.

Eccrine and Apocrine Sweat glands

- Eccrine sweat glands are simple tubular glands which possess a coiled section located in the lower dermis.
- There are approximately 3,000,000 on the body.
- Eccrine sweat glands secrete fluid which consists of 99% water with other minor components such as proteins, lipoproteins, lipids and several saccharides.
- The pH of the secretion is about 5.

- The skin is driest at its surface, with a water content of 10 to 25%, and a pH of between 4.2 and 5.6.
- The lower epidermal layers contain up to 70% water and the pH gradually increases to 7.1 to 7.3.
- The “acid mantle” derives from the lactic acid and carboxylic amino acids in the sweat secretions mixed with the sebaceous secretions.

- The lower fatty acids (propionic, butyric, caproic or caprylic) have been demonstrated to have fungistatic and bacteriostatic action, possibly due to the low pH which they produce.

- The isoelectric point of keratin is between 3.7 and 4.5 and hence materials applied to the skin should have a pH greater than this value.

Passage of Drug Through The Skin

Routes of absorption

- Drug diffusion from a transdermal delivery system to the blood can be considered as passage through a series of diffusional barriers.
- The drug has to pass first from the delivery system through the SC, the epidermis and the dermis, each of which has different barrier properties.
- Differences in composition of these layers cause them to display different permeabilities to drugs, depending on molecular properties such as diffusion coefficient, hydrophobicity, and solubility.

- The first limiting factor for absorption of the drug is the vehicle or device.
  - In a transdermal drug delivery device, the primary design goal is the maintenance of the desired constant drug concentration at the skin surface for a suitable length of time.
- The second and major barrier for most compounds is the SC.
  - Skin from which SC has been removed is highly permeable, while the removed SC is nearly as impermeable as the entire skin.
  - Skin from cadavers has approximately the same permeability as living skin, suggesting that the underlying tissues present little resistance to drug absorption.

- The final barrier is the living portion of the epidermis and the dermis.
  - Diffusion rates in these viable tissues are much higher than in the SC and consequently they offer little resistance to absorption.
- However, the tissues are much more hydrophilic than the SC, and so act as a barrier to extremely hydrophobic compounds which cannot partition into them.
- As a result transdermal absorption is optimal for compounds with intermediate polarity which can pass through both the SC and dermal tissues.

- Absorption can occur through several possible routes on an intact normal skin.

A. Trans-appendageal

- Through the hair follicles
- Through sweat/sebaceous glands

B. Trans-epidermal

- Between the cells of horny layer
- Through the epidermal layer

- Trans-appendageal absorption is often considered unimportant
- However, it is more rapid than trans-epidermal transport, and so provides a loading dose, which is sustained by slower diffusion through the epidermis
- There are two possible routes of passage of drugs through the SC;
  - Via the hydrophilic keratinised cells or
  - Via the lipid channels organized largely in bilayers between the cells.
- The lipoidal nature of the lipid channels favours passage of hydrophobic molecules, and since many drugs are hydrophobic, this is their major route of entry

- Transdermal drug absorption is influenced considerably by the degree of hydration of the skin, probably due to a combination of several factors including improved contact or wetting, and hydration of the lipid channels of the SC.
- Application of oily materials can improve the skin hydration by reducing the evaporation of moisture from underlying tissues.
- Hydration increases the penetration of polar molecules more than nonpolar ones
  - So it is possible that hydration of the lipid channels is more important than hydration of keratinised cells.

- It is possible to hydrate the lipids in the SC (despite their hydrophobic nature) because they contain a large fraction of surface-active ‘polar lipids’ which are surfactant-like in nature (for example, phospholipids)
- The SC can act as a reservoir for drugs, causing the pharmacological response to continue for a short time after the device has been removed.
- If the skin is then allowed to dry out, the drug will diffuse into underlying tissues more slowly, and application of an occlusive patch which rehydrates the skin can cause release of the drug at a later time.

Advantages and disadvantages of topical/transdermal delivery

- Advantages
  - Drugs applied transdermally avoid the chemically hostile GI environment containing acid, food and enzymes.
  - If there is GI distress, disease, or surgery.
  - First-pass metabolism of the drug is avoided since the blood drains directly into the main venous return.
  - Patient compliance is good.
  - They can provide a sustained plasma profile over several days.

- Disadvantages
  - Drugs may be metabolized by bacteria on the skin surface.
  - Enzymatic activity in the epithelium may be different to that in the GIT, leading to unexpected routes of breakdown of drugs.
  - Maintaining contact between a drug delivery device and the skin could be difficult.
  - Application of the device occludes the skin, trapping water and sebum from the glands.
  - The transdermal route can cause drug sensitization.

Factors Affecting Drug Absorption through the Skin

- **Individual variation**
  - Dosage must be titrated to achieve a therapeutic benefit
  - And the transdermal system does have the advantage in this respect that treatment can be stopped rapidly if too great a response is observed.
- **Age**
  - Skin condition and structure varies with age
  - The SC is not fully developed in neonates
  - In older people the SC thickens and is less hydrated, increasing its barrier function.

- **Site of Application**
  - Drug absorption varies greatly with site of application.
  - Heavily keratinized sites, notably the arch of the foot, are several times less efficient than the forearm.
  - It has been suggested that the site of application of the delivery device should be varied to reduce the skin sensitivity.
- **Occlusion**
  - Occlusion increases adsorption considerably in many cases, probably due to increased hydration of the SC, improving permeability to both polar and non-polar drugs.
  - The increased humidity under the dressing may increase the bacterial load hence potential bacterial degradation of the drug needs to be studied.

- **Temperature**
  - Temperature affects drug penetration by two mechanisms:
    - Firstly it alters the physiology of the skin, and
    - Secondly the physicochemical diffusion rates in the device increase with temperature
  - The skin temperature is strongly influenced by its surroundings, and may be 20 °C cooler than body temperature or several degrees hotter
  - Temperature also influences blood flow in the surface vasculature and so might be expected to influence adsorption through this route.

- **Race**
  - Race appears to influence penetration to a small extent.
  - Negroid SC has more layers and is generally less permeable, although there is no difference in actual thickness between negroid and European SC.
  - It is not known if the presence of melanocytes influences the penetration of drugs.
- **Disease**
  - Any damaged or diseased area of the skin is likely to display compromised barrier properties and consequently higher drug absorption
  - Presence of disease may disrupt structural integrity of SC

Penetration Enhancers

- Transdermal absorption is relatively slow, and needs materials which will increase the penetration rate of drugs through the skin.
- Penetration enhancers are believed to operate by increasing the permeability of the SC, either in the lipid or the keratinized protein regions.
  - The largest class of penetration enhancers appear to fluidize the lipid channels.
  - A further possibility for penetration enhancement is to influence the nature of the lipid channels by altering lipid biosynthesis in the skin.

- Two approaches for enhancing drug penetration:
  - **Passive Methods of Enhancing**
    - These entails the optimization of formulation or drug carrying vehicle to increase skin permeability

    E.g. Chemical enhancers, Supersaturated systems, Liposomes and other vesicles

- **Active Methods of Enhancing**

  - In contrast to passive methods, active methods, normally involving physical or mechanical methods of enhancing delivery have been shown to be generally superior.

  - Involve the use of External Energy to act as a driving force and/or act to reduce the barrier nature of the SC.

  E.g. Iontophoresis, Electroporation, Microneedles, Abrasion, Needleless Injection, Stretching, Ultrasound, Magnetophoresis, Radio Frequency, Lasers, Photomechanical Waves, And Temperature Manipulation

Chemical Enhancement

- Some chemical excipients when included in transdermal formulations can enhance the permeability of drugs through a number of mechanisms such as:
  - Increasing the solubility of drug in the vehicle and hence increasing the total delivered dose from a single application.
  - Increasing drug solubility in the SC, that is, facilitating partitioning of drug from the vehicle into the skin.
  - Reducing the diffusional barrier of the SC by either perturbing the intercellular lipid domains or to a lesser degree perturbing the intracellular keratin networks.
  - Promoting drug partitioning at the SC - viable tissue interface.

- The following criteria should be met for an excipient to be used as a penetration enhancer:
  - The chemical excipient should not have inherent pharmacological activity
  - The permeation enhancement should be specific
  - Reversible
  - Have good chemical and physical stability
  - Be compatible with the rest of the components of the drug delivery system
  - Should be devoid of toxic, allergic, and irritation potential and should be classified as a ‘generally recognized as safe’

- E.g. Sulfoxides, alcohols, polyols, alkanes, fatty acids, esters, amines and amides, terpenes, surfactants, cyclodextrins, etc.

Physical (Active) Enhancement

E.g. Iontophoresis, Electroporation, Microneedles, Abrasion, Needleless Injection, Stretching, Ultrasound, Magnetophoresis, Radio Frequency, Lasers, Photomechanical Waves, And Temperature Manipulation

- Read … (Assignment I, to be submitted)

Ointment

- Definition
- Properties
- Ointment bases (Properties, Selection criteria, Types)
- Preparation, Packaging, Labeling, and Storage

- Ointments are semisolid preparations intended for topical application.
- They are used to provide **protective** and **emollient** effects on the skin or **carry medicaments** for treating certain topical ailments
- They are also used to deliver drugs into eye, nose, vagina, and rectum
- Desired properties of dermatological preparations also applies to ointments

Ointment Bases

- In ointment formulations, the active ingredient is incorporated into a carrier system - the vehicle, called 'Base'

- Ointment bases are classified based on their composition and physical characteristics.

- The U.S. Pharmacopeia (USP) classifies ointment bases as:

1. Hydrocarbon bases (oleaginous bases)
2. Absorption bases
3. Water - removable bases, and
4. Water - soluble bases (water - miscible bases)

- There are some selection criteria for ointment bases:
  - Desired release rate of the drug
  - Rate and extent of absorption
  - Desirability of occlusion of moisture
  - Compatibility with other components (effect of the base on the drug and other components, and vice versa)
  - Physicochemical and microbial stability of the product, and ease of manufacture

- Pourability and spreadability of the final formulation, and duration of contact
- Easy removal of base on washing
- Chances of hypersensitivity reactions and irritation potential
- Characteristic of the surface to which it is applied

1. Hydrocarbon bases

- These are made of oleaginous materials.
- They provide emollient and protective properties and remain in the skin for prolonged periods.
- It is difficult to incorporate aqueous phases into hydrocarbon bases.
- Removal of hydrocarbon bases from the skin is difficult due to their oily nature.
- E.g. Petrolatum (Vaseline), Paraffin, Mineral oil

- Main characteristics of hydrocarbon bases:
  - They are not absorbed by the skin
  - They are water immiscible, and their water absorption potential is low
  - They are sticky
  - They are almost inert
  - Cheap and readily available

2. Absorption bases

- These contain small amounts of water, and can absorb considerable amount of water
- They provide relatively less emollient properties than hydrocarbon bases
- Similar to hydrocarbon bases, absorption bases are also difficult to remove from the skin due to their hydrophobic nature
- E.g. Hydrophilic Petrolatum, Anhydrous Lanolin, Hydrous Lanolin (W/O emulsion base)

3. Water - removable (Water-miscible) bases

- These are basically O/W emulsions.
- Unlike hydrocarbon and absorption bases, a large proportion of aqueous phase can be incorporated with the aid of suitable emulsifying agents.
- It is easy to remove these bases from the skin due to their hydrophilic nature.
- E.g. Hydrophilic ointment USP

4. Water - soluble bases

- These do not contain any oily or oleaginous phase.
- Solids can be easily incorporated into these bases.
- They may be completely removed from the skin due to their water solubility.
- E.g. Polyethylene glycol (PEG)

Sources, physicochemical properties, formulation considerations, stability, incompatibility, storage, and hypersensitivity reactions of commonly used ointment bases

Lanolin

- Lanolin is a refined, decolorized, and deodorized material obtained from sheep wool (wool fat).
- It is available as a pale yellow, waxy material with a characteristic odor.
- It is extensively used in the preparation of hydrophobic ointments and water - in – oil creams.

- As lanolin is prone to oxidation, antioxidants are generally included.
- Although lanolin is insoluble in water, it is miscible with water up to 1:2 ratio. This property favors in preparing physically stable creams
- Addition of soft paraffin or vegetable oil improves the emollient property of lanolin preparations.
- Exposure of lanolin to higher temperature usually leads to discoloration and rancid-like odor
    - Gamma sterilization or filtration sterilization is usually employed for sterilizing ophthalmic ointments containing lanolin

- Lanolin and some of its derivatives are reported to cause hypersensitivity reactions
  - One of the reasons for hypersensitivity reactions is free fatty alcohols
  - Modified lanolins containing reduced levels of free fatty alcohols are commercially available

Hydrous Lanolin

- Produced by incorporation of about 25 – 30% of water into lanolin
- Gradual addition of water into molten lanolin with constant stirring helps in water incorporation.
- It is available as a pale yellow, oily material with a characteristic odor.
- The water uptake capacity of hydrous lanolin is higher than lanolin, and it is used for preparing topical hydrophobic ointments or W/O creams

- Exposure of hydrous lanolin to higher temperatures results in separations of oily and aqueous layers

- Addition of antioxidants and preservation in well - filled, airtight, light - resistant containers in a cool and dry place improve the stability of lanolin products

- Hydrous lanolin that contains free fatty alcohols is avoided in hypersensitive patients

Lanolin Alcohols

- Lanolin alcohol is prepared from lanolin by the saponification process
- It is composed of steroidal and triterpene alcohols
- Available as a **brittle solid material**, and it becomes plastic under warm conditions.
- It is practically insoluble in water and soluble in boiling ethanol
- It possesses emollient properties
- Lanolin products should be preserved in well - filled, well - closed, light - resistant containers in a cool and dry place, can be stored up to two years

Lanolin

Lanolin Alcohol

Petrolatum

- Petrolatum (Vaseline) is also known as yellow soft paraffin
- It is an inert material obtained from petroleum
- It is available as soft oily material and appears pale yellow to yellow in color
- Various grades of petrolatum are commercially available with varying physical properties
- Its generally insoluble in water and possess emollient properties

- Petrolatum shows phase transitions on heating to about 35°C, prolonged heating is avoided during processing
- The presence of minor impurities can oxidize petrolatum and discolor the product
  - Antioxidants are, therefore, added to prevent such physical changes in preparations during storage.
- In addition, use of well - closed, airtight, light - resistant containers and storage in a cool and dry place improve stability of preparations.
- Petrolatum sometimes cause hypersensitivity reactions due to impurities. Substituting yellow soft paraffin with white soft paraffin reduces such reactions

Petrolatum and Lanolin Alcohols

- Various quantities of lanolin alcohols are mixed with petrolatum to form these mixtures
- These proportions can be varied to alter physical properties such as consistency and melting range
- These mixtures are insoluble in water, and concentrations ranging 5-50% are used for preparing hydrophobic ointments

Paraffin

- Paraffin is obtained by distillation of crude petroleum followed by purification processes
- The purified fraction contains saturated hydrocarbons
- Paraffin is available as a **white color solid** and does not possess any specific odor or taste
- Different purity grades are available
- Use of highly purified grades can avoid batch - to - batch variations in formulations, especially the hardness, melting behavior, and malleability

- Paraffin is insoluble in water and is generally used to prepare hydrophobic topical ointments and W/O creams
- Repeated heating and congealing are avoided during formulation as they change the physical properties of paraffin
- These preparations need to be preserved in well - closed container at room temperature
- Synthetic paraffins, which melt between 96 and 105 °C, are sometimes used to increase the melting point and stiffness of formulations

Polyethylene Glycol (PEG)

- Also known as **macrogol**, PEG is synthesized by *condensation of ethylene oxide and water* under suitable reaction conditions
- Described by numbers referring their average molecular weights
- They are available as liquids, semisolids or solids based on molecular weight
- PEGs 600 or less is liquids, whereas PEGs above 1000 are semisolids and solids

- PEGs are hydrophilic materials and are extensively used in the preparation of hydrophilic ointments and creams.
- They are non-irritants and are easily washed from skin surfaces.
- Excessive heating is avoided while melting PEGs. This will prevent oxidation and discoloration of products.
- In addition, use of purified grades that are free from peroxide impurities, inclusion of suitable antioxidants, and heating under nitrogen atmosphere can minimize the oxidation

- They are incompatible with some antibiotics, antimicrobial preservatives, iron, tannic acid, and salicylic acid and also interact with plastic containers made of PVC and PE

- PEG - containing products are usually packed in aluminum, glass, or stainless steel containers to avoid such interactions

- Although low molecular weight PEGs are hygroscopic, they do not promote microbial growth.

- These products can cause stinging sensation on mucus and some hypersensitivity reactions, especially when applied onto open wounds

Stearic Acid

- Stearic acid is obtained by hydrolysis of fat or hydrogenation of vegetable oils
- It is available as **powder or crystalline solid** which is white to yellowish white in color and possesses a characteristic odor
- Although stearic acid is insoluble in water, partially neutralized grades form a cream base when combined with about 10 times its weight of aqueous solvents
- Different grades of stearic acids are commercially available

- A suitable antioxidant is included in formulations containing stearic acid
- As stearic acid interacts with metals, it is avoided in preparations which contain salts, especially divalent metals such as calcium and zinc
- It also reacts with metal hydroxides and some drugs
- Compatibility evaluation between stearic acid and other formulation components is therefore essential when formulating newer products with stearic acid

Carnauba Wax

- Carnauba wax contains a mixture of esters of acids and hydroxyacids isolated from Brazilian carnauba palm.
- It is available as lumps, powder, or flakes which are brown to pale yellow in color and possesses a characteristic odor.
- Carnauba wax is practically insoluble in water and melts at 80-88 °C.
- Being a hard material; it improves the **stiffness** of topical preparations

Cetyl Alcohol

- Cetyl alcohol is obtained by hydrogenolysis or esterfication of fatty acids
- It is available as flakes or granules white in color and possesses a characteristic odor
- Different grades are commercially available
- Although insoluble in water, cetyl alcohol has good water - absorptive and emulsifying properties
- This property makes it suitable for preparing emollient ointments and creams

- Its viscosity – enhancing properties reduce coalescence of dispersed phase and improves the physical stability of creams
- Concentrations ranging from 2 to 10% are used in topical preparations to impart emollient, emulsifying, water - absorptive and stiffening properties
- Mixtures of petrolatum and cetyl alcohol are sometimes used for preparing creams.
- Although cetyl alcohol forms stable preparations, it is incompatible with strong oxidizing materials and some drugs
- Highly purified grades are free from hypersensitivity reactions

Emulsifying Wax

- Emulsifying wax, also known as **anionic emulsifying wax**, is a mixture of cetostearyl alcohol, sodium lauryl sulfate, and purified water
- It is available as flakes or solids which are white to pale yellow in color and possesses a characteristic odor
- Although emulsifying wax is insoluble in water, its emulsifying properties help in preparing hydrophilic O/W emulsions.
- Although emulsifying wax is compatible with many acids and alkalis, it is incompatible with many cationic materials and polyvalent metal salts.
- Stainless steel vessels are preferred for mixing operations.

Cetyl Esters Wax

- This is obtained by esterification of some fatty alcohols and fatty acids.
- It is available as crystalline flakes and possesses a characteristic aromatic odor.
- It is insoluble in water and has emollient and stiffening properties.
- Various grades of cetyl esters wax are available commercially
- As this wax is incompatible with strong acids and bases, it should be avoided in certain formulations.

Hydrogenated Castor Oil

- It is used as stiffening agent in hydrophobic ointments and creams due to its higher melting point.
- It contains triglyceride of hydroxystearic acid
- It is insoluble in water and melts at 85-88 °C.
- Different grades with varying compositions and physical properties are commercially available.
- Products can be prepared at higher temperatures, as hydrogenated castor oil is stable up to 150 °C.

Microcrystalline Wax

- Microcrystalline wax is obtained from petroleum by solvent fractionation and dewaxing procedures.
- It contains many straight chain and branched chain alkanes
- It is available as fine flakes or crystals which are white or yellow in color.
- It is insoluble in water and possesses a wide melting range (54-102 °C).
- Acids, alkalis, oxygen, and light do not affect its stability

Stearyl Alcohol

- Reduction product of ethyl stearate
- It is available as flakes or granules which are white in color and possesses a characteristic odor.
- It is insoluble in water and melts at 55 – 60 °C.
- Stearyl alcohol has stiffening, viscosity - enhancing, and emollient properties and hence is used in the preparation of hydrophobic ointments and creams
- Its emulsifying properties help in improving the water - holding capacity of ointments.

Yellow Wax

- Yellow wax, also known as yellow beeswax, is obtained from honey combs.
- It is available as non-crystalline pieces which are yellow in color and possesses a characteristic odor.
- It is practically insoluble in water and melts at 61 – 65 °C.
- Esterification occurs while heating to 150 °C and hence should be avoided during preparation.
- Concentrations up to 20% are used for producing ointments and creams.

White Wax

- White wax is a **bleached** form of yellow wax which is usually obtained from the honeycomb of bees and hence is known as bleached wax or white beeswax.
- It is available as granules or sheets which are white in color and possesses a characteristic odor.
- It is insoluble in water and melts between 61 and 65°C.
- White wax and yellow wax have stiffening and viscosity - enhancing properties and therefore are used in hydrophobic ointments and oil - in - water creams.
- White wax and yellow wax are incompatible with oxidizing agents.

Other ingredients of Ointment Bases

- **Vegetable Oils**
  - May be added as: Softening agents or to increase Emolliency
  - Penetrate the skin more readily than paraffins, but less well than wool fat
  - Prone to oxidation
  - E.g. Arachis Oil, Olive Oil, Castor Oil, Coconut Oil

- **Synthetic Esters of Fatty Acids**
  - More constant in composition than vegetable oils
  - Resistant to oxidation, and hydrolyze less readily
  - Substitute vegetable oils
  - E.g. Isopropyl myristate
  - Serve as a solvent for many topical medications

- **Higher Fatty Alcohols**
  - Included in ointment base for:
    - They have good emollient properties but are not greasy
    - They facilitate incorporation of water
    - They are readily absorbed by the skin and don’t rancidify

- **Silicones**
  - Their water – repellency is of value in barrier ointments
- **Polar Organic Solvent**
  - When the ointment contains much less of the drug (e.g. some corticosteroid products), these solvents are added to ensure uniform dispersion and maximum release of the drug
  - They are also added when the drug is insoluble in the base

Preparation of Ointments

- A good ointment product is;
  - Uniform throughout:
    - Contains no lumps
    - No tendency for liquid constituent to separate
    - Insoluble powders are evenly dispersed
  - Free from grittiness:
    - Insoluble powders are finely subdivided
    - Large lumps of particles are absent

- Any method of shall try to address these criteria
- Different techniques are employed to incorporate the API and different additives into the ointment base.
- In compounding of ointments, the following general considerations are observed:
  - If insoluble substances are to be incorporated in the ointment base then they should be in impalpable powder form
  - For efficient incorporation of insoluble substances they should first be levigated with a little quantity of base to form a smooth cream and then incorporated into the remainder of the base

- Water-soluble salts are best incorporated by dissolving them in a small quantity of water and then incorporating in the base
- Drugs soluble in ointment bases may also be incorporated by fusion. Remaining ingredients are then added and mixed by stirring

- The two most frequently used methods in preparing ointments are:

A. Mechanical incorporation method

B. Fusion method

A. Mechanical incorporation method (Lavigation or Trituration)

- Involves simple mixing of base and other components over an ointment slab using a stainless steel ointment spatula
- Finely subdivided insoluble medicaments are evenly distributed by grinding with a small amount of the base or one of its ingredients followed by dilution
- Part of the base may be used as a levigating agent

B. Fusion method

- Ingredient are melted together and stirred to ensure homogeneity
- The fusion method is employed when:
  - The components are stable at fusion temperatures
  - Drugs and other solids are soluble in the ointment bases
- Selection of mechanical incorporation or fusion method depends on:
  - The type of base
  - The quantity of components
  - Solubility and Stability characteristics

Equipments used for ointment preparation

- **Equipments for fusion method**
  - Small scale fusion generally carried out in an evaporating basin of porcelain or stainless steel

1. Glazed porcelain basins
   - Not attacked by the substance commonly presented
   - Light color & smooth surface can be seen to be spotlessly clean before use
   - Its fragile , and heat transfer is relatively is poor

Fig. Porcelain basin

2. Metal basins of stainless steel type

- Virtually indestructible
- Heat transfer is good
- React only with few pharmaceuticals

Fig. Stainless steel basin

- **Equipments for mechanical incorporation method**

1. Mortar & Pestle

- Made from **unglazed** porcelain
- Flat internal base mortal & flat head pestle
- Used in compounding when large quantities of liquids are to be incorporated or when large quantities of the ointments are to be prepared.

Fig. Mortar and Pestle

2. Ointment Tile (slab) and Spatula

- **Tile/Slab**
  - May be made from porcelain or glass
  - And should be large enough to prevent spillage (usually 30x30cm)
  - Commonly - glass tiles built into benches & illuminated from below are used to facilitate inspection for lumps and grittiness
- **Spatulas** (larger and smaller)
  - Usually stainless steel type

- Larger spatula
  - Should be flexible
  - Should have a broad, no tapering long blade (usually 2.5x20 cm)
    - This provide large rubbing surface
- Smaller spatula
  - This is used for removing accumulated material from the larger

Fig. Larger and Smaller spatulas

- Iron, Stainless steel or Vulcanite spatulas are available
  - Selection depends on he there are not the substances will attack the materials
  - Vulcanite types are commonly used for substances that cause corrosion

Mortar Vs Tile:

- It is easier to transfer the product from a tile
- If quantity of the product is larger, mortar is preferred
- If a liquid is to be incorporated, mortar is preferred

3. Ointment mill

- Ointment mills are particularly suitable for large scale manufacture of ointments although small mills are available for laboratory scale ointment preparation

- Ointments containing gritty particles are also passed through the ointment mill to ensure further uniformity and smoothness

Fig. Ointment Mill (Lab scale)

Ointment preparation by Fusion method

A. Unmedicated Ointments

- When ointment base contain different ingredients with **varying** MP,
  - Melt in **descending** order of their MP, and this will be:
    - Quicker
    - Require less heat
    - Avoid over heating
  - After melting, continue stirring until cold

- Take care of localized cooling of the preparation
  - To prevent localized cooling, we need to avoid:
    - Using a cold spatula or stirrer
    - Placing the dish/basin on a cold surface
    - Transferring to a cold container before the ointment has fully set
  - If these are ignored, hard lumps may separate
  - And if this occurred, re-melt using minimum heat and stir until cold

NB: Avoid vigorous stirring after the ointment has begun to thicken. This will cause excessive **aeration**.

B. Medicated Ointments

- Solids that are completely or partially **soluble** in the fused base, are finely powdered first and added to previously melted base, and stir until cold.

- **Liquids** and **semisolids** are incorporated just as the base starts thickening (at about 40 ^{O}C) (why?)

- When a solid is **soluble in a liquid** ingredient it may be more convenient to add it in solution

- **Insoluble** solids are first passed through a **No-180 sieve** and added in small amounts to the melted base when it shows the first sign of **thickening** (take care of sedimentation)

Ointment preparation by Mechanical incorporation

- Best applicable when the medicament is either:
  - Solid and insoluble in the base or
  - Liquid and present in small amount or
  - Thermo labile

- Powders for incorporation by trituration are placed on a tile or a mortar
  - And gently but efficiently mixed
  - Vigorous grinding should be avoided, because this may cause impaction
- Liquid ingredients are incorporated at the final stage – to avoid loss from splashing
  - Better to incorporate in a mortar

- If the base is not very soft, it is advantageous to warm the equipment
  - Avoid excessive heating – the base will become too fluid for efficient levigation
- Levigate the powder only with two to three times its weight of the base

- If a large amount of lavigating agent is used for levigation,
  - Attrition between the particles & between the particles and the levigating surface is reduced
  - Satisfactory preparation made more difficult, and greater effort is required
  - Uniform distribution is uncertain

Preparation of oleaginous ointments

- Oleaginous ointments are prepared by both levigation and fusion processes
- Powders are incorporated with the aid of a lavigating agent
- The powder component is mixed with the LA by trituration and is then incorporated into the base by spatulation - by geometric dilution

Preparation of absorption ointments

- Water - insoluble drugs can be added by mechanical addition or fusion methods
- LA may be used
  - If the drug needs to be incorporated into the internal aqueous phase - Water-soluble/miscible agents are used as LA
  - If the drug needs to be incorporated into the external oily phase - mineral oil is used as LA

- If the proportion of aqueous phase is larger:
  - Include additional emulsifier
  - Apply heat, but should not be excess (why?)

Preparation of water - removable ointments

- These are prepared by fusion followed by mechanical addition
- Hydrocarbon components are melted together and added to the aqueous phase that contains water - soluble components
- A hydrophilic emulsifying agent is included in the aqueous phase in order to obtain **stable** oil - in - water dispersion.

Preparation of water - soluble ointments

- These ointment preparations do not contain any oily phase
- Both levigation and fusion methods can be used for preparation
- If the drug and other components are water-soluble, they are dissolved in a small quantity of water and incorporated into the base by spatulation
- If the components are insoluble in water, aqueous levigating agents such as **glycerin** are used
- Heat aids incorporation of a large quantity of hydrophobic components

Packaging, Labeling & Storage of ointment preparations

- The problems of stability of ointments are mostly concerned with the initial and 'in-use' microbial contamination.
- Many ophthalmic ointments are found to be heavily contaminated with pathogenic micro-organisms.
- The main source of microbial contamination in ointments is water which supports the growth of micro-organisms.

- To safeguard the stability of the packaged ointment product the following points are borne in mind:
  - In general, the pharmacist or the manufacturer should follow Good Manufacturing Practice (**GMP**).
  - Use of **preservatives** to protect against the contamination, deterioration or spoilage of ointment bases.
  - Use of **antioxidants** when there is possibility of oxidative degradation of the base.
  - Use of **chelating agents** where the presence of traces of metallic ions is anticipated. The traces of metallic ions, if present, may catalyze oxidative degradation.

- The immediate container should not permit evaporation of water from the packaged ointments
    - Otherwise an emulsion base may lose aqueous phase and others may become dry and hard.
- The containers should ensure not only the sterility of ophthalmic ointments initially but also up to a time till whole of the preparation is consumed.
- Due to wide variations in the climatic conditions in different regions, maintenance of desirable consistency of an ointment is also an important consideration.

- Ointments are traditionally packaged in jars and collapsible tubes.
  - The jars are made of glass that is either green or opaque white.
  - Ordinary collapsible tubes are convenient to the patient because they are easier to carry and do not break when they are dropped.
  - Collapsible tubes are especially valuable for ointments that lose moisture or decompose on exposure to the atmosphere.

Ointment Jar

Ointment collapsible tubes

Filling Ointment Jars

- Ointment jars, avail
- May be filled by o them with a small spatula.
- In packing, the sic way around should be covered first, addin center and top in order to minimize air pock
- Melted ointments c y to settle out may be poured into contain id.
- In either case, the oothed off at the top before the lid is clos

Filling Ointment Tubes

- Ointment tubes can be pharmacy by first rolling the ointment into a glassin aper to make a cylinder just smaller than the base of

  - Remove the cap of the air will not be trapped when the ointment is inserted.

  - Insert the roll, ointment nbined, as far into the tube as the roll will go and close it b :ening the end of the tube.

  - Hold the end of the tul firm pressure from the side of a spatula and carefully p ne paper out of the tube. The ointment is left in the tul

  - Fold the end of the tube ease it tightly, and score it several times with the spatula ec it from opening during use.

- Note:
  - Ointments made by fusion may be poured directly into the tubes.
  - Stored at temperatures below 30 ^{o}C to prevent softening
- An ideal container should:
  - Protect the product from the external atmosphere such as heat, humidity, and particulates
  - Be non-reactive with the product components
  - Be easy to use
  - Light in weight, and
  - Economical

Labeling of ointment products

- Select a label corresponding in size to the size of the jar being used.
- Metal ointment tubes should be moistened with tincture of benzoin before the label is applied to help the label adhere.
- When the label has been put into place, it should be covered with a strip of cellophane tape.
- The auxiliary label **"For External Use Only"** is required on all ointments, pastes, and creams.

Storage

- Storage of semisolids should be at temperatures not exceeding 25 °C unless otherwise authorized.
- They should not be allowed to freeze and must be stored in a well-closed container.
- Preparations containing water or other volatile ingredients must be stored in an air-tight container.
- The containers are preferably collapsible metal tubes from which the preparation may be readily extruded.
- If the preparation is sterile (e.g. ophthalmic ointment), store in a sterile, airtight, tamper-proof container.

- Definition and storage/test conditions for four climatic zones

Climatic zones	Definition	Storage/test conditions	Example
I	Temperate climate	21°C±2°C and 45% ±5% RH	Northern Europe, Canada
II	Mediterranean & subtropical climate	25°C±2 °C and 60%±5% RH	Southern Europe, Japan, US
III	Hot & dry climate	30°C±2°C and 35% ± 5% RH	Egypt, Sudan
IV	Hot & humid climate	30°C±2°C and 75% ±5% RH	Central Africa, South Pacific

Tests requirements for ointments

1. Microbial Content

- Meet acceptable standard for microbial content
  - The ointment product must be free of *Staphylococcus aureus* and *Pseudomonas aeriginosa*
- Must contain antimicrobial preservatives
  - E.g. Methylparaben, propyl paraben, phenols, benzoic acid, quaternary ammonium salts

2. Minimum Fill Test

- Check for net weight and volume

3. Packaging, Storage, and Labeling requirements

- Well closed, air tight, light resistant containers
- Labeling

4. Additional Standards

- Examine the viscosity and pourability
- *In vitro* drug release to ensure content uniformity

Pastes

- Definition
- Properties of pastes
- Methods of preparation
- Packaging, Labeling and Storage

- **Pastes** are semi-solid preparation for external application that differ from similar products, like ointments, in containing high proportion (about 50%) of finely divided powders.
- Stiffer than ointments which make them useful as protective agents
- They are emollient but, porous (because of their high powder content) – and perspiration can escape

- When pastes are applied to the skin:
  - Less greasy than respective ointments,
  - Confine to the applied area,
  - Adhere well and form a thick coat,
  - Protect and soothe inflamed and raw surfaces,
  - The powder can absorb exudates, and less macerating

- Pastes are not cosmetically accepted:
  - A thick layer is to be applied
  - To be applied generously
  - Are not to be removed for longer periods
- Basically pastes are ointments, but only with a larger proportion of particulate solids (like starch, talc, ZnO, and $CaCO_3$
  - This stiffens the system
    - By direct interaction of dispersed particles
    - By adsorbing the liquid fraction within the vehicle

- Insoluble ingredients are used as dispersed phase, like starch, talc, ZnO, and $CaCO_3$
- Generally less greasy than respective ointments because of the adsorption of the liquid HC fraction
- Pastes are good protective barriers when applied to the skin, forming unbroken film
- The solid absorb & neutralize certain noxious substances (can be applied to ameliorate Diaper Rash)

Packaging, Labeling & Storage of Paste preparations

- Pastes are prepared in a similar method as ointments
- Packaging, Labeling & Storage of paste preparations are similar to that of ointment preparation

Creams

- Definition
- Types of creams
- Properties of creams
- Methods of preparation
- Packaging, Labeling and Storage

- **Creams** are semi-solid preparation for external application.
- They are intended to be applied to the skin or certain mucous membranes especially when occlusive effect is **not** necessary.
  - Creams are formulated to provide preparations that are essentially miscible with skin secretion.
- Creams are basically ointments which are made less greasy by incorporation of water.
  - Presence of water in creams makes them act as emulsions and therefore are sometimes referred as **semisolid emulsions**.

- Creams have a **creamy appearance** as a result of reflection light from their emulsified phase
  - This differs them from ointments which are **translucent**
- The term 'Cream' may be applied to:
  - Absorption bases containing emulsified water (W/O Emulsions)
  - Semisolid O/W Emulsions (because of their cream appearance)
- Not all preparations with creamy appearance are creams
  - The term 'cream' is reserved exclusively for **semisolid emulsions**

- As with ointments, creams are formulated to provide protective, emollient actions or deliver drugs to surface or interior layers of skin, rectum, and vagina.

- Creams are softer than ointments and are preferred because of their easy removal from containers and good spreadability over the absorption site.

Types of Creams

- Depending on the emulsion type:
  - **Hydrophilic creams** (O/W creams) contain large amounts of water in their external phase (e.g. Vanishing cream)
  - **Hydrophobic creams** (W/O creams) contain water in the internal phase (e.g. Cold cream)
- An emulsifying agent is used to disperse the aqueous phase in the oily phase or vice versa

- A semisolid O/W types of creams are selected, because:
  - Readily diluted with water
  - Non - staining
  - Ease of application
  - Volatile components may evaporate, and thin application shrinks to an even thinner layer, leaving the drug forming a film
    - Be careful of drying-out, because this will cause precipitation of the drug
    - Ensure that the formed film has some capacity to dissolve its drug (add low-volatile, water miscible solvents)

Packaging, Labeling & Storage of cream preparations

- Creams are prepared in a similar method as ointments
- Packaging, Labeling & Storage of cream preparations are similar to that of ointment preparation

Jellies and Gels

- Definition
- Properties of Jellies and Gels
- Methods of preparation
- Packaging, Labeling and Storage

- **Gels** are semisolid system in which a liquid phase is constrained/trapped within an interlocking 3-D polymeric matrix having a high degree of physical or chemical cross-linking.

OR

- Semisolid preparations consisting of dispersions made up of either inorganic particles or large organic molecules enclosing or inter penetrating by a liquid.

- **Jellies** are transparent or translucent non-greasy semisolid gels.
  - A gel rich in liquid may be called a **jelly**

- If the liquid is removed and only the gel framework remains this is termed a **xerogel**.

- Gels may be one phase or two phase systems
  - **One phase**
    - Where the macromolecules are distributed throughout the liquid in such a manner that no apparent boundaries exist between them.
  - **Two phase**
    - Where the gel mass consists of floccules of small distinct particles
- Most gels are transparent and aesthetically pleasing taste.
- Some are turbid because the polymer present in colloidal aggregates that disperse light.

- Because of their larger water content, gels are:
  - Suitable for water soluble drugs, but less satisfactory for lipophilic substance
  - Easy to apply
  - Evaporation of water content produces a pleasant cooling effect
  - The residual film adheres well
  - Easily removed by washing

- The majority of gels are formed by aggregation of colloidal sol particles
- The particles link together to form an interlaced network, thereby imparting rigidity to the structure; the continuous phase is held within the meshes.
- The vehicle is continuous and interacts with the colloidal particles within the 3-D network that is formed by the bonds formed between adjacent particles.
- The vehicle may be aqueous, hydro alcoholic, alcohol based or non-aqueous.

- There are two main categories of pharmaceutical gels, based on the nature of the three-dimensional network of particles:

    1. Dispersed solids

    2. Hydrophilic polymers (Type I and Type II gels)

Gels based on dispersed solids

- In certain conditions dispersed solids will undergo flocculation.
- If flocculation extends throughout the system a continuous solid particle network is established, with the liquid vehicle dispersed in the void volume between the particles.
- The nature of the interaction between the particles in the network may be Vander Waals interactions
    - However, for certain dispersed solids the nature of the interaction is electrostatic bonding.

Gels based on hydrophilic polymers

- Most pharmaceutical gels are manufactured by dispersing hydrophilic polymers within an appropriate aqueous vehicle.
- Hydrophilic polymers behave as lyophilic colloids in aqueous vehicle.
  - With unique physical properties result from the self-association of the dissolved polymer and its interaction with the aqueous medium.
- There are two types of self-association (termed irreversible and reversible) and based on this we have either **Type I** or **Type II** gels.

- **Type-I gels** (Hydrogels) are **irreversible** systems
  - 3-D network formed by **covalent bonds** between the macromolecules.
  - Such polymers have been used in the fabrication of expanding implants that imbibe body fluids and swell to a predetermined volume.
  - Implanted in the dehydrated state, these polymers swell to fill a body cavity or give form to surrounding tissues.
  - They also find use in the fabrication of implants for the prolonged release of drugs, such as antibiotics, into the immediate environment of the implant.

- These gels exhibit unique physicochemical properties:
  - The ability to absorb a considerable mass of aqueous fluid (often 100 times the original mass) whilst still retaining a 3-D structure.
  - Exhibit robust mechanical properties, being resistant to fracture following exposure to stresses.
  - Moreover, they exhibit excellent flexibility.

- **Type II gels** are held together by much weaker intermolecular bonds such as hydrogen bonds, ionic association or van der Waals interactions.

- The application of stresses to type-II gels will end in the temporary destruction of these bonds, thereby enabling the formulation to flow.

- As a result, type-II gels are rheologically referred to as pseudoplastic (shear-thinning) systems.

- Following the removal of the stress, the inter-macromolecular bonds are reformed and the viscosity of the formulation returns to its equilibrium value.

- These gels are heat reversible, a transition from the sol to gel occurring on either heating or cooling.

- Poly vinyl alcohol solutions, for example, gel on cooling below a certain temperature referred to as the gel point.

  - Because of their gelling properties poly vinyl alcohols are used as jellies for the application of drugs to the skin.

  - On application the gel dries rapidly, leaving a plastic film with the drug in intimate contact with the skin

- The majority of pharmaceutical gels are type-II gels
- The following polymers are employed in the formulation of these systems:
  - **Cellulose derivatives** (E.g. methylcellulose (MC), hydroxyethylcelluloses (HEC), hydroxypropylcellulose (HPC), sodium carboxymethylcellulose (SCMC)
  - **Polysaccharides derived from natural sources** (E.g. carrageenan (a polysaccharide from red seaweed) and alginic acid/sodium alginate (a polysaccharide that is derived from algae)
  - **Polyacrylic acid**

- Factors affecting gelation of type-II gels

1. Concentration of hydrophilic polymer

- At low concentrations, solutions of such polymers exhibit Newtonian flow due to the limited number of polymer–polymer interactions.

- As the concentration of polymer increases, the number of polymer–polymer interactions increases and eventually, at a defined polymer concentration (termed the gel point), the flow properties of these systems become non-Newtonian.

- Further increases in the concentration of the polymer lead to an increase in the number of junction zones and hence the resistance to deformation from an applied stress increases.

2. Molecular weight of the polymer

- As the molecular weight of the hydrophilic polymer increases (at a defined concentration of polymer), there are a greater number of available sites on the polymer chains that may engage in polymer–polymer interactions.

- As a result the viscosity of the formulation increases.

3. Nature of the solvent

- In solvents that are described as '**good solvents**', the chains of a polymer will exist in the expanded state.

- Conversely, in the presence of a **poor solvent**, the polymer chains will exist in a non expanded (coiled) state.

- The viscosity of a polymer solution is dependent on the expansion of the polymer chains.

4. pH of the solvent

- The pH of the solvent directly affects the ionization of acidic or basic polymers which, in turn, affects the conformation (expansion) of the polymer chains.

5. Temperature

- Certain hydrophilic polymers may undergo a thermally induced transition that results in an increase in the rheological properties.

- **Formulation considerations** in the preparation of gels:
  - **Choice of vehicle**
    - Purified water is the normal solvent/vehicle used in the formulation of pharmaceutical gels.
    - However, co-solvents (like alcohol, propylene glycol, glycerol, and polyethylene glycol) may be used to enhance the solubility of the therapeutic agent and to enhance drug permeation across the skin.
  - **Inclusion of buffers**
    - May be included in aqueous and hydro-alcoholic based gels to control the pH of the formulation

- **Preservatives**
  - It should be remembered that certain preservatives (like parabens, phenolics) interact with the hydrophilic polymers, thereby reducing the concentration of free (active) preservative in the formulation.
  - Therefore, to compensate for this, the initial concentration of these preservatives should be increased.
- **Antioxidants**
  - Antioxidants may be included in the formulation to increase the chemical stability of therapeutic agents that are prone to oxidative degradation

- **Flavoring/sweetening agents**
  - These are included in gels that are designed for administration into the oral cavity
- **Colorants**
  - These are added to impart some unique colors to increase cosmetic acceptance

Preparation of pharmaceutical gels

- Gels are relatively easier to prepare compare to ointments and creams.
- In the manufacture of pharmaceutical gels, generally the water-soluble components are initially dissolved in the vehicle in a mixing vessel with mechanical stirring.
- The hydrophilic polymer must be added to the stirred mixture slowly to prevent aggregation and stirring is continued until dissolution of the polymer has occurred.

- Some of the factors to be considered to obtain a uniform gel preparation are discussed below.
  - **Order of mixing**
    - In addition to the gelling agent, medicated gels contain drug, antimicrobial preservatives, stabilizers, dispersing agents, and permeation enhancers.
    - The order of mixing of these ingredients with the gelling agent is based on their influence on the gelling process.

- If they are likely to influence the rate and extent of swelling of the gelling agent, they are mixed after the formation of gel.

- In the absence of such interference, the drug and other additives are mixed prior to the swelling process.

- Ideally the drug and other additives are dissolved in the swelling solvent, and the swelling agent is added to this solution and allowed to swell.

- **Gelling medium**
  - Purified water is the most widely used dispersion medium in the preparation of gels.
  - Under certain circumstances, gels may also contain cosolvents or dispersing agents.

- A mixture of ethanol and toluene improves the dispersion of ethylcellulose (EC).
- Dichloromethane and methanol increase the viscosity of hydroxypropyl cellulose (HPC) dispersions.
- Alcohol improves the rheological stability of polyethylene oxide gels.
- Inclusion of glycerin, propylene glycol, sucrose, and alcohol improves the dispersion of sodium alginate dispersions.

- **Processing conditions**
  - The processing temperature, pH of the dispersion, and duration of swelling are critical parameters in the preparation of gels.
  - These conditions vary with each gelling agent.
    - For instance, hot water is preferred for gelatin and polyvinyl alcohol, and cold water is preferred for methylcellulose dispersions.

- Carbomers, guar gum, hydroxypropyl cellulose, poloxamer, and tragacanth form gels at weakly acidic or near - neutral pH conditions (pH 5 – 8).

- Gelling agents such as carboxymethyl cellulose sodium, hydroxypropylmethyl cellulose (HPMC), and sodium alginate form gels over a wide pH range (4 – 10).

- Hydroxyethyl cellulose forms gel at alkaline pH condition.

- **Duration of swelling**
  - A swelling duration of about 24 – 48 hours generally helps in obtaining homogeneous gels.
  - Natural gums need about 24 hours and cellulose polymers require about 48 hours for complete hydration.

- **Removal of entrapped air**
  - Entrapment of air bubbles in the gel matrix is a common issue.
  - It should be noted that excessive stirring of pharmaceutical gels results in entrapment of air.
    - Especially when the swelling process involves a mixing procedure or the drug and other additives are added after the swelling process.

Packaging, Labeling and Storage of Gels

- Being viscous and non - Newtonian systems, gels need high attention during packing into containers.
- Usually they are packed into squeeze tubes or jars made of plastic materials.
- Aluminum containers are also used when the product pH is slightly acidic.
- Pump dispensers and prefilled syringes are sometimes used for packing gels.
- As most of the gels contain an aqueous phase, preservation in **airtight containers** helps in protecting them from microbial attack.

Evaluation of Gels

- Some of the tests recommended by the USP for gels include, Minimum fill, pH, Viscosity, Microbial screening.
- **pH**
  - Many gelling agents show pH - dependent gelling behavior.
  - They show highest viscosity at their gel point.
  - Determination of pH is important to maintain consistent quality.

- **Viscosity**
  - Viscosity measurement is often the quickest, most accurate, reliable method to characterize gels.
  - It gives an idea about the ease with which gels can be processed, handled, or used.
  - Viscometers measure the frictional force that is created when gels start flowing.

- **Homogeneity and Surface Morphology**
  - The homogeneity of gel formulations is usually assessed by visual inspection.
  - The surface morphology is studied using scanning electron microscopy.

- **Stability Studies**
  - Being dispersed systems containing water in their matrix, gels are prone to physical, chemical, and microbial stability issues.
  - **Syneresis** is a commonly observed physical stability problem with gels.
    - It involves squeezing out of dispersion medium due to elastic contraction of polymeric gelling agents.
    - This results in shrinkage of gels.

Rheologic Properties and Drug Release from Semisolid Dosage Forms

- Assignment II

Rheologic Properties of Semisolid Dosage Forms

- Rheology studies to describe the flow of liquids and the deformation of solids
- The fundamental principles of rheology are of practical importance in pharmacy
  - Manufacturers of semisolid preparations must be capable of producing products with acceptable consistency and smoothness and reproducing these qualities each time a new batch is prepared.
- The rheology of a particular substance can affect: its patient acceptability, Physical stability, Biologic availability, and Selection of processing equipment

- In the world of semi-solid material, rheological properties such as yield stress, thixotropy, and viscoelasticity have a direct impact on pharmaceuticals, foods, cosmetics, and consumer products.

- Semi-solid materials exhibit liquid and solid like properties depending on temperature, as well as on being subjected to stress and strain over time.

  - Since these materials act like elastic solids under some conditions and viscous liquids under others, they are viscoelastic materials.

- Knowledge of the rheological properties is important for design and process evaluation, process control, and consumer acceptability of a product.

- Most semisolids are of complex rheological nature, and their viscosity depends not only on temperature and composition, but also on shear stress, shear rate, time of shearing, as well as on the previous shear and thermal history.

- Processes such as new ingredient selections, formulation preparations, material packaging, and shelf storage are associated with a complex flow of materials.

- In general, rheological measurements on pharmaceutical and cosmetic materials are performed for the following reasons:
  - To understand the fundamental nature of a system
  - For quality control of raw materials, final products, and manufacturing processes such as mixing, pumping, packaging, and filling
  - To study the effect of different parameters such as formulation, storage time, and temperature on the quality and acceptance of a final product.
- Semisolid products are the most difficult materials to characterize rheologically because they combine both liquid and solid properties within the same material.

Steady shear flow curves

- A flow curve, viscosity versus shear rate, can provide important information about storage stability; optimal conditions for mixing, pumping, and transferring; and end-user applications.

- It also provides important information regarding the ways in which the structure changes to comply with the applied shear in different conditions, such as storage, processing, and application.

- The rheological behavior of the material may change as a result of these forces.

- If the shear rate changes during an application, the internal structure of the sample will change and the change in stress or viscosity can then be seen.
  - Newtonian flow is the simplest type, displaying a shear-independent viscosity while the material is sheared.
  - Pseudo-plastic or shear thinning fluids display viscosity reduction while the shear rate increases.
  - Dilatant or shear thickening flow, in which viscosity increases with shear rate.
    - This is seldom encountered in the pharmaceutical and cosmetics fields.

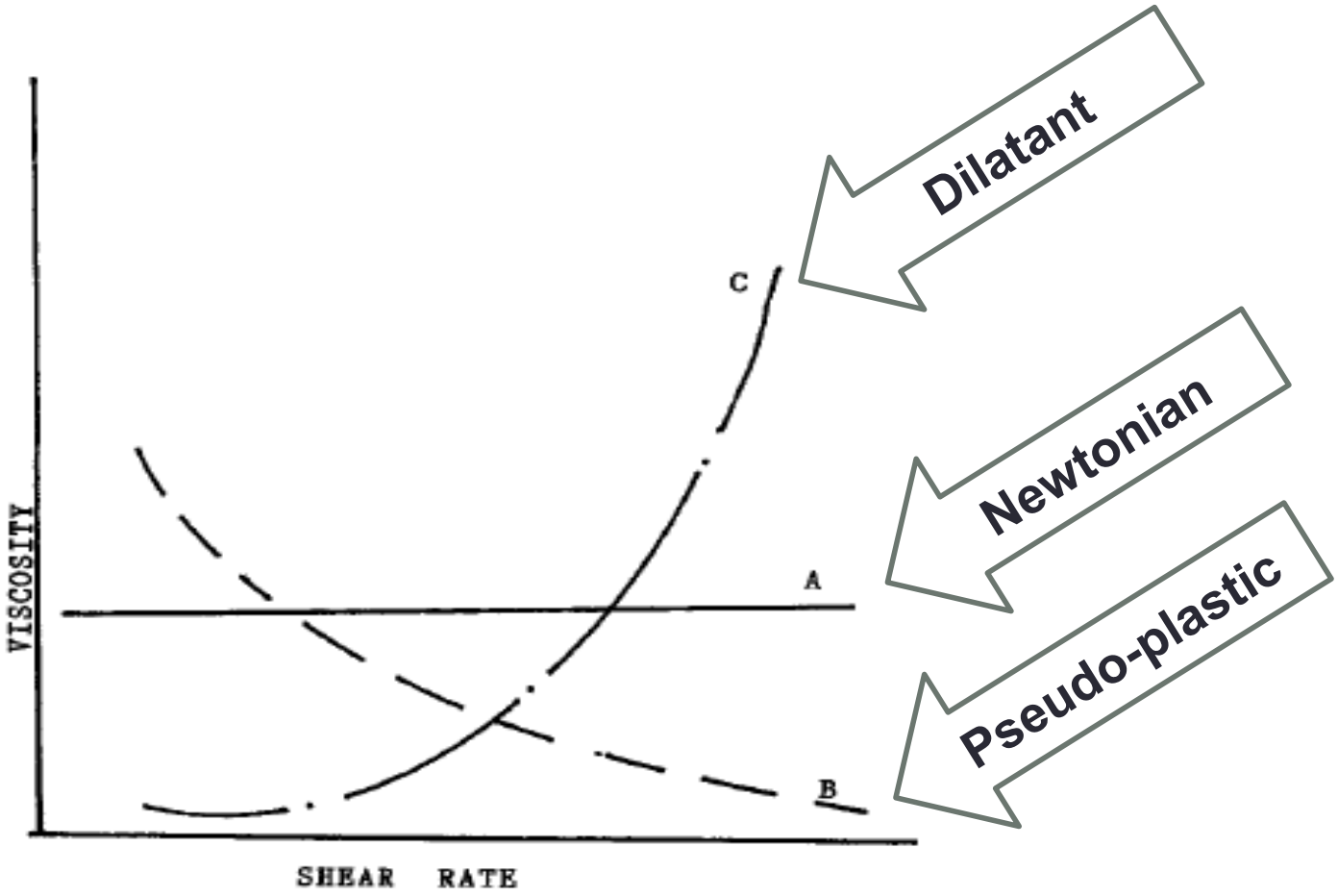


Fig. Typical flow curves.

Thixotropy

- Time-dependent flow measures the increase or decrease in viscosity with time, while a constant shear is applied.
- The flow is called thixotropic if viscosity decreases with time, or rheopetic if it increases.
- The most desirable type of flow behavior encountered in pharmaceutical or cosmetic products is thixotropic flow.
- Thixotropic behavior describes a degradation of the structure during the loaded phase; thus, a reduction in viscosity with time occurs when shear is applied.

- During the relieved phase, the original structure is recoverable.
  - The extent of structural recovery is dependent on the time allowed for the recovery.
  - Therefore, a thixotropic material will have a shear thinning behavior when a gradually increasing shear is applied.
  - This is because the orientation of the structure's molecules or particles will change to align with the flow direction.
- However, its original orientation can be restored over a period of time after the external force is removed.
- There is a delay in time for the structure to recover completely.

Yield stress

- The yield stress measurement is crucial for pharmaceutical products in determining not only their shelf life but also ease of application for the end user.
- Yield stress is the minimum shear stress required to initiate flow.
- Yield stress can also be defined as the stress below which a material will not exhibit a fluid-like behavior.
  - This means that subjecting a material to stresses less than the yield stress will lead to a nonpermanent deformation

- The concept of yield stress is only an approximation since this stress value is experimental time dependent.
- Almost all substances will eventually flow if the time scale for imposing a shear stress (however small) is long enough.
- The magnitude of the yield stress value may be used as one of the criteria for controlling sedimentation during storage and the ease of using or processing a product.
    - E.g. The higher the static yield value, the more readily a medium will maintain particles in suspension with minimal sedimentation.

- Semisolids do not flow at low shear stresses but undergo reversible deformation like elastic solids.
- When a characteristic shear stress, called the yield value or yield stress, is exceeded, they flow like liquids.
- Yield stresses usually are caused by structural networks extending throughout an entire system.
  - To break such a network requires stress, which will produce no flow but only elastic deformation.
  - When the yield stress is exceeded, the network is partly ruptured and flow occurs.

- Semisolids with high yield values are described as “hard”.
- When their plastic viscosity is high, they are described as “stiff”.
- Best instrument for determining the rheologic properties of pharmaceutical semisolid is some form of a rotational viscometer e.g. Cone-plate, Cup and Bob viscometers etc.

Drug Release from Semisolid Dosage Forms

- Reading assignment (??)